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EXAMINER

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CHERESKIN, C

ART UNIT

PAPER NUMBER

15

1804

DATE MAILED:

10/02/92

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on Jan. 30, 1990 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|--|
| 1. <input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892. <i>lp</i> | 2. <input type="checkbox"/> Notice re Patent Drawing, PTO-948. |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, Form PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> _____ |

Part II SUMMARY OF ACTION

1. ☒ Claims 1-4, 7, 15-18 are pending in the application.
Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 5-6, 8-14 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-4, 7, 15-18 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with Informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received
☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

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EXAMINER'S ACTION

Claims 1-4, 7, and 15-18 remain. Claims 5-6, 8, and 9-14 are cancelled.

The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office action.

- 5 The rejection under 35 U.S.C. 112 second paragraph on page 2 of the previous office action is withdrawn in view of Applicants' amendments.

Claim 18 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- 10 Does the "native sequence" in claim 18 encompass only the HD-1 Dipel subsp. kurstaki BTS sequence or any native B.t. delta endotoxin sequence?

- 15 Claims 1-4, 7, and 15-18 are rejected under 35 U.S.C. 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- 20 The specification teaches determination of codons preferentially used by plant genes with reference to Figure 1. However, the claims read on any method of determining codons which are "preferentially utilized by the native plant genes" (claim 1, for example). Not all tables of codon usage are identical and vary depending upon the genes used to compile the information. For example, since many of the first genes sequenced were storage protein genes, the data in some tables is based upon a disproportionate number of storage protein genes which may not be typical of plant genes in general. This rejection could be overcome by reference to Figure 1 in the claims. For example, amendment of claim 1 to read "selected from among the codons determined from Figure 1 to be preferentially utilized by the native plant genes" is suggested.
- 25

The specification is objected to and claims 1-4, 7, and 15-18 remain rejected under 35 U.S.C. 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention for the reasons set forth in the previous office action. Applicants' arguments have been considered but are not deemed persuasive.

It is not apparent that the modified B.L. sequences work significantly better than the native sequences. As set forth previously, the distribution of clones into the "9" rating is slightly higher for the synthetic constructs, but it is not clear what criteria were used to establish the various categories 6-9. Furthermore, since the majority of the control plants fell into the "8" category, the relevant question, which does not appear to be addressed in the specification, is whether or not the difference between an "8" and a "9" rating is significant.

Applicants argue that it is not legally relevant under 35 USC 112 whether or not the synthetic sequences worked better than native sequences (Response, pages 3-4, bridging paragraph). This argument is not persuasive as "The specification must set forth the precise invention for which a patent is solicited, in such a manner as **to distinguish it from other inventions and from what is old**" 37 CFR 1.71(b), emphasis added.

Applicants argue that the details of their rating system are not necessary to practice the claimed invention (Response, pages 4-5, bridging paragraph). While this may be true, it is maintained that the particulars of the difference between the "9" rating and the "8" rating seem to be the only factor that separates Applicants' claimed invention from what is known, and what this difference entails is not set forth anywhere in the application.

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The rejection of claims 1-14 under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to Manduca sexta is withdrawn in view of Applicants' amendments.

5 The rejection of claims 1-17 under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to claims which recite the upper sequence shown in Figure 2 is withdrawn in favor of the new ground of rejection set forth below.

10 Claims 1-4, 7, and 15-18 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to B.t. delta-endotoxin protein genes derived from genes encoding B.t. delta-endotoxin proteins from about 130 to 140 kD. See MPEP 706.03(n) and 706.03(z).

15 As taught by Hofte et al B.t. crystal proteins differ in many characteristics such as size, structure, and insect specificity (see Tables 1, 3, and 5, and Figures 1 and 2, for example). Since B.t. crystal proteins constitute such a diverse group, it is not predictable that techniques applied to one group would be applicable to other groups. While the present claims are limited to products which show toxicity against Manduca sexta, this limitation is insufficient as it is noted that diverse crystal proteins have toxicity against Lepidopteran insects (see Table 1, for example).

20 Given this unpredictability, the limited guidance presented in the specification, and the breadth of the claims, it is deemed that undue experimentation would be required of one skilled in the art to practice the invention as so broadly claimed, and that the claims should be limited to B.t. delta-endotoxin protein genes derived from genes encoding B.t. delta-endotoxin proteins from about 130 to 140 kD as disclosed in the Examples of
25 the instant specification.

Claims 1-4, 7, and 15-18 remain rejected under 35 U.S.C. 103 as being unpatentable over Hoekema et al taken with Grantham et al, Schnepf et al,

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Vaeck et al, Barton et al, Hollenberg et al, and Seeburg et al as applied in the previous office action. Applicants arguments have been carefully considered but are not deemed persuasive.

5 As recited previously, Hoekema et al teach a method of affecting gene
expression by exploiting codon usage. Hoekema et al disclose that when
foreign proteins are used in yeast vector systems the expression level may
decrease one or two orders of magnitude. Hoekema et al teach that the
codon choice pattern was one parameter affecting this low level of
expression and that expression of native highly expressed yeast genes can be
10 altered by substituting the codons usually found in yeast genes with minor
codons which never or rarely occur in highly expressed natural genes. The
amino acid sequence was not disturbed. As a result, both mRNA and protein
synthesis were decreased.

15 Hoekema et al differ from the claimed invention primarily in that
their work was directed to yeast cells, not plant cells as in the claimed
invention. However, modification of a procaryotic sequence to optimize
expression in a plant cell was well within the ordinary level of skill in the art
as shown by Grantham et al (see especially, Tables 1 and 2). More
specifically, in Bacillus thuringiensis as reported by Schnepf et al, it was
20 known that the use of A or T was preferred. It was also known that B.
thuringiensis toxins in particular were poorly expressed in plant cells as
reported for example by Vaeck et al and Barton et al. Furthermore, Barton
et al teach the expression of insect toxins in tobacco using the pAMVBTS
vector. Thus, it would have been obvious to one of ordinary skill in the art
25 that the concept taught by Hoekema et al in yeast could be applied to
expression of foreign genes in plants by modification of known vectors for
expression of Bt toxins such as those taught by Barton et al and Vaeck et al
in accordance with the guidelines provided by Hoekema et al and Grantham
et al.

Methods of transfer of foreign genes to plant cells and expression in plant cells were all well within the ordinary level of skill in the art. Methods of making long oligonucleotides were known in the art as taught by Hoekema et al, Hollenberg et al (Figure 9), and Seeburg et al (Figure 2).

5 Applicants argue that no reference cited shows a gene with increased expression (Response, page 6, paragraph 2). In response, Applicants do not show that genes with increased expression can be predictably obtained for genes within the scope of the claims. As pointed out under 35 USC 112,
10 paragraph 1, the specification is not convincing that Applicants teach a reproducible method of improving expression in plants. Consequently, Applicants' claimed genes are obvious over unmodified B.t. genes. With reference to Table 1, although, the distribution of clones into the "9" rating is slightly higher for the synthetic constructs, it is not clear what criteria were used to establish the various categories 6-9. Furthermore, since the majority
15 of the control plants fell into the "8" category, the relevant question, which does not appear to be addressed in the specification, is whether or not the difference between an "8" and a "9" rating is significant.

Applicants argue that plants and yeast are different and that Hoekema et al changed 15% of the codons in the coding region to obtain 96% preferred
20 codons while Applicants only changed 10% of the codons to achieve 10-25% preferred codons for an effect on expression (Response, pages 6-7, bridging paragraph). This argument is not persuasive as the claimed invention is not distinguished from the prior art B.t. genes and corresponding transgenic plants for reasons discussed in the preceding paragraph and because, even if
25 Applicants' results are unexpected, they are not commensurate with claim scope.

In conclusion, while a comparison of column 1 and 2 may reflect differences in transformation frequency rather than efficacy of the modification, it is maintained that the data of Table 1 are not convincing

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when the differences between the "9" rating and the "8" rating are not set forth in the specification.

Thus, the rejection set forth previously clearly sets forth a prima facie case of obviousness which has not been overcome by Applicants' arguments.

- 5 The rejection is therefore maintained as the method of improving expression and dicot plants with improved expression are obvious over the prior art, absent evidence to the contrary.

No claim is allowed.

- 10 An inquiry concerning this communication should be directed to Che Swyden Chereskin, Ph.D., at telephone number (703) 308-1180. Inquiries of a general nature should be directed to the Group 180 secretary at (703) 308-0196.

- 15 Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

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CHE S. CHERESKIN
PATENT EXAMINER
GROUP 180

Che Swyden Chereskin
9/24/92

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